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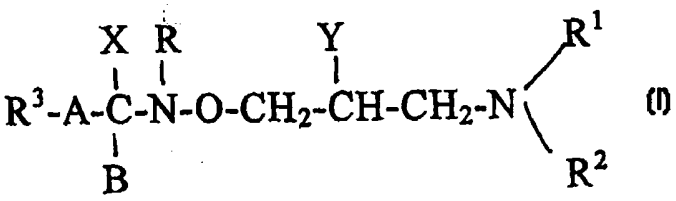
(57) Abstract

The invention refers to pharmaceutical compositions having an enhanced antiviral activity and/or decreased side effects. The composition comprises a hydroximic acid derivative of formula (I), or a therapeutically useful acid addition salt thereof and a known antiviral agent or, if desired, a therapeutically useful acid addition or therapeutically useful salt thereof.



(I)

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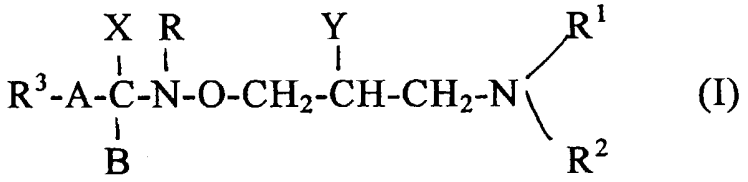
PHARMACEUTICAL COMPOSITION WITH ANTIVIRAL ACTIVITY CONTAINING AN HYDROXYMIC ACID DERIVATIVE AND AN ANTIVIRAL AGENT

The invention relates to an antivirally pharmaceutical composition exerting an enhanced antiviral action and/or decreased side effect(s).

Antivirally active agents used e.g. for the treatment of HIV viral infections induce a general cellular injury in addition to the primary virus-injuring effect. Consequently, in a number of cases the chance of survival of the organism weakened also by the viral infection is hardly improved.

The hydroximic acid derivatives of formula (I)



(I)

wherein

R^1 means hydrogen or C_{1-5}alkyl group;

R^2 represents hydrogen; C_{1-5}alkyl group; C_{3-8}cycloalkyl group; or phenyl group optionally substituted by hydroxyl or phenyl group; or

R^1 and R^2 together with the adjacent nitrogen atom form a 5 to 8 membered ring optionally containing additional nitrogen, oxygen or sulfur atom(s); and

said ring can be condensed with an other alicyclic or heterocyclic ring, preferably with benzene, naphthalene, quinoline, isoquinoline, pyridine or pyrazoline ring; furthermore if desired and possible, nitrogen and/or sulfur as heteroatom(s) are present in the form of an oxide or dioxide;

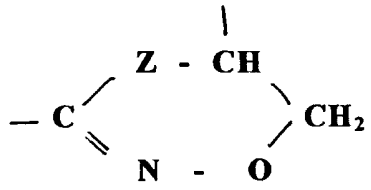
R^3 stands for hydrogen or phenyl, naphthyl or pyridyl group optionally substituted by one or more halogen(s) or C_{1-4}alkoxy group(s);

Y means hydrogen; hydroxyl group; C_{1-24}alkoxy group optionally substituted by amino group; C_{2-24}polyalkenyloxy group containing 1 to 6 double bond(s); C_{1-25}alkanoyl group; C_{3-9} alkenoyl group; or a group of formula R^7-COO-, wherein R^7 is a C_{2-30}polyalkenyl group containing 1 to 6 double bond(s);

X represents halogen; amino group; or C_{1-4}alkoxy group;or

X and B together form an oxygen atom; or

X and Y together with the adjacent carbon atoms and the interjacent -NR-O-CH_2- group form a ring of formula (a),



(a)

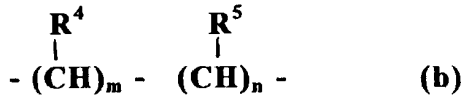
wherein

Z means oxygen or nitrogen;

R means hydrogen; or

R and B together represent a chemical bond;

A stands for C_{1-4}alkylene group or a chemical bond; or a group of the formula (b),



(b)

wherein

R^4 means hydrogen; C_{1-5}alkyl group; C_{3-8}cycloalkyl group; or a phenyl group preferably substituted by halogen, C_{1-4}alkoxy or C_{1-5}alkyl group;

R^5 means hydrogen; C_{1-4}alkyl group; or a phenyl group;

m is 0, 1 or 2; and

n is 0, 1 or 2,

The US-PS No. 4,308,399 discloses compounds belonging to the scope of hydroximic acid derivatives of formula (I), which are useful for treatment of the diabetic angiopathy.

The EP-PS No. 417,210 describes hydroximic acid halides, which also fall into the scope of compounds of formula (I), possess a selective ß-blocking effect and are useful for treatment of the diabetic angiopathy.

The Hungarian published patent application No. T/66350 discloses a number of other hydroximic acid derivatives being within the scope of compounds of formula (I). These known

substances are useful in the therapy of vascular complications, particularly of diabetes mellitus.

It is known from the PCT Application No. WO/9713504 that hydroximic acid derivatives of formula (I) are useful for the prevention and treatment of disorders of mitochondrial origin. According to an investigation discussed in the description rats were treated with zidovudine (AZT), an antiviral nucleoside analogue useful in the therapy of AIDS, in order to correct the "defect" of the mitochondrial genom. This method resulted in animals suffering from hereditary cardiomyopathy. It was concluded from this investigation that the studied compounds of formula (I) diminished or prevented the mitochondrial membrane-injuring effect of zidovudine. However, it cannot be concluded from this establishment in any way that compounds of formula (I) were useful to diminish or to eliminate the unfavourable side effect of all known antivirally active substances.

The aim of the invention is to provide a pharmaceutical composition, which exerts an enhanced effect in comparison to that of the known antivirally active agent and/or decreases the side effects of the known antivirally active agent.

It has been found that the above aim can be achieved by the pharmaceutical composition according to the invention, which comprises a known antivirally active agent or, if desired and possible, a therapeutically useful acid addition salt thereof or therapeutically useful salt thereof, and a hydroximic acid derivative of formula (I), wherein R, R^1, R^2, R^3, A, B, X and Y are as defined above, or a therapeutically useful acid addition salt thereof together with one or more usual carrying materials.

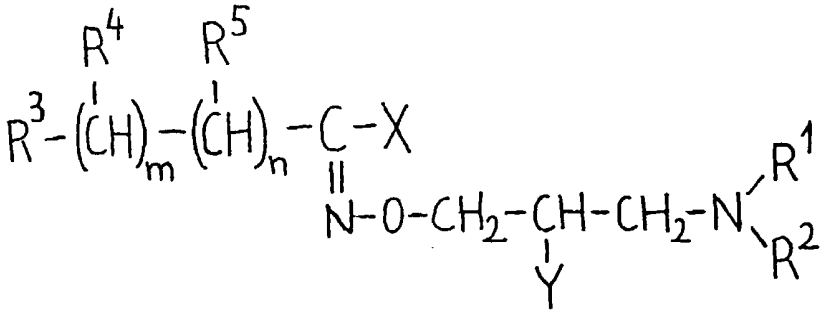
Within the meanings of substituents defined in relation to the formula (I):

- C_{1-5}alkyl represents e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, or n-pentyl group, preferably methyl or ethyl group;
- C_{3-8}cycloalkyl stands e.g. for cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl group, preferably cyclonpentyl or cyclohexyl group;
- the 5 to 8 membered ring may be e.g. pyrrole, pyrazole, imidazole, oxazole, thiazole, pyridine, pyridazine, pyrimidine, piperazine, morpholine, indoline, quinoline ring or the like;
- the C_{1-24}alkoxy group may be e.g. methoxy, ethoxy, n-propoxy, tert-butoxy, n-pentoxy, decyloxy, dodecyloxy, octadecyloxy group or the like;
- the C_{1-25}alkanoyl group may represent e.g. formyl, acetyl, propionyl, butyryl, caproyl, palmitoyl or stearoyl group and the like;
- the C_{3-9}alkenoyl group means e.g. acryloyl, pentenoyl, hexenoyl, heptenoyl, octenoyl group or the like;
- the C_{1-4}alkylene group may be e.g. methylene, ethylene, propylene or butylene group;
- halogen may mean e.g. fluorine, chlorine, bromine or iodine, preferably chlorine or bromine.

Y as R^7-COO- group may be e.g. linolenoyl, linoloyl, docosahexanoyl, eicosapentanoyl or arachidonoyl group or the like.

The physiologically (therapeutically) useful acid addition salts of the compounds of formula (I) are meant to be acid addition salts formed with therapeutically suitable inorganic acids, e.g. hydrochloric or sulfuric acid and the like; or with therapeutically useful organic acids, e.g. acetic, fumaric or lactic acid and the like.

Within the compounds of formula (I), a preferable subclass consists of hydroximic acid derivatives of formula (II),



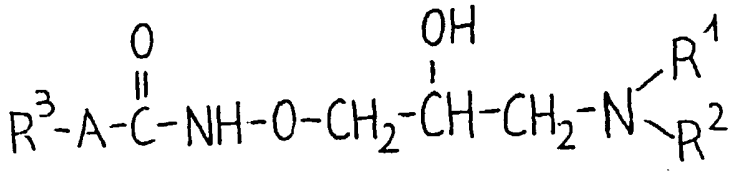
II

wherein R^1, R^2, R^3, R^4, R^5, m and n are as defined for formula (I); X means halogen or amino group; and Y stands for hydroxyl group.

Compounds of formula (II), wherein R^1 and R^2 together with the adjacent nitrogen atom form a piperidino group, R^3 is a pyridinyl group, both m and n are 0, and X is as defined above, are particularly preferred. Of these

0-(3-piperidino-2-hydroxy-1-propyl)nicotinic acid amid-oxime dihydrochloride (compound "L") is especially suitable.

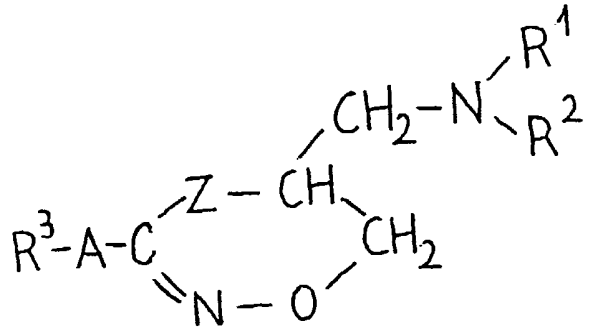
An other advantageous subclass of the compounds of formula (I) consists of the compounds of formula (III),



III

wherein R^1, R^2, R^3 and A are as defined for formula (I).

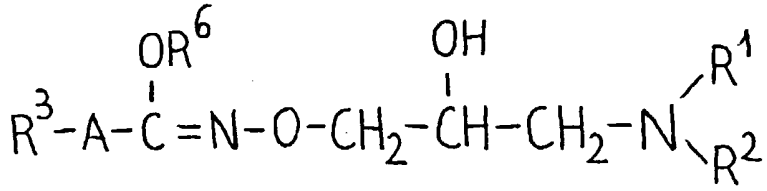
A third preferred subclass of hydroximic acid derivatives of formula (I) includes cyclic compounds of formula (IV)



IV

wherein R^1, R^2, R^3 and A are as defined for formula (I), and Z means oxygen or nitrogen.

A fourth preferred subclass of hydroximic acid derivatives of formula (I) comprises compounds of formula (V),



V

wherein R^1, R^2, R^3 and A are as defined for formula (I) and R^6 stands for C_{1-4}alkyl group.

The compounds of formula (I) can be prepared by using processes known from US-PS No. 4,308,399 and EP-PS 417,210.

Known antivirally active agent (substance) is meant to be an antivirally active substance inhibiting the viral DNA polymerase, viral genom transcription, RNA polymerase, reverse transcriptase, helylase, primase, integrase, viral protein translation, the formation (developing) of viral regulating protein or viral structural protein and the like. The viral protease inhibitors are also included herein.

On the basis of chemical structure, the known antivirally active agents are chiefly purine and pyrimidine derivatives, nucleosides and nucleotides. Without limiting the possible known antivirally active agent of the pharmaceutical composition according to the invention to those listed below, preferred active agents of such type are e.g. as follows:

acyclovir: 9-[(2-hydroxyethoxy)methyl]-9H-guanine,

valacyclovir: L-valyl ester of acyclovir,

pencyclovir: 9-[4-hydroxy-3-(hydroxymethyl)-but-1-yl]guanine,

famcyclovir: diacetyl ester of pencyclovir,

gancyclovir: 9-(1,3-dihydroxy-2-propoxymethyl)guanine,

idoxuridine: 2'-deoxy-5-iodouridine,

floxuridine: 2'-deoxy-5-fluoruridine,

sorivudine: 1ß-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil,

trifluridine: 5-trifluoromethyl-2'-deoxyuridine,

vidarabine: 9ß-D-ribofuranosyladenine,

zidovudine (AZT): 3'-azido-3'-deoxythymidine,

didanosine: 2',3'-dideoxyinosine,

zalcytabine: 2',3'-dideoxycytidine,

cytarabine: 4-amino-1-D-arabinofuranosyl-2(1H)-pyrimidinone,

dideoxyadenosine: 2',3'-dideoxyadenosine, and

edoxudine: 2'-deoxy-5-ethyluridine and the like.

The known antivirally active agent can be used also in the form of its therapeutically useful acid addition salt, if its chemical structure allows the preparation of an acid addition salt. Similarly, the known antivirally active agent may be used as its therapeutically suitable salt, e.g. metal salt, ammonium salt or salts formed with organic bases, when its chemical structure is suitable for the preparation of such salts.

The pharmaceutical composition of the invention possessing an enhanced antiviral activity contains preferably zidovudine as antivirally active agent (ingredient); and 0-(3-piperidino-2-hydroxyl-1-propyl)-nicotinic acid amidoxime or a therapeutically useful acid accition salt thereof as a hydroximic acid derivative of formula (I).

The pharmaceutical composition according to the invention commonly contains the active ingredients in amounts of 0.1 to 95% by weight, preferably 1 to 50% by weight, suitably 5 to 30% by weight together with the usual carrier(s) of pharmaceutical compositions.

In the pharmaceutical composition according to the invention, the weight ratio of the two active ingredients is preferably (1 to 50) : (50 to 1), particularly preferably (1 to 10) : (10 to 1).

The pharmaceutical composition of the invention can be a solid or liquid composition usefor for oral, parenteral or rectal administration or topical treatment.

The solid pharmaceutical compositions useful for oral administration can be powders, capsules, tablets, film-coated tablets, microcapsules and the like; and may contain as carrier(s) binders, e.g. gelatine, sorbitol, polyvinylpyrrolidine and the like; filling materials, e.g. lactose, glucose, starch, calcium phosphate and the like; tabletting aids such as magnesium stearate, talc, polyethylene glycol, silicon dioxide and the like; as well as wetting agents, e.g. sodium lauryl sulfate and the like.

The liquid pharmaceutical compositions for oral administration are solutions, suspensions or emulsions containing as carriers e.g. a suspending agent, such as gelatine, carboxymethylcellulose and the like; emulsifying agents, e.g. sorbitan monooleate; solvents such as water, oils, glycerol, propylene glycol, ethanol; as well as preservatives such as methyl or propyl p-hydroxybenzoate and the like.

The pharmaceutical compositions for parenteral administration are usually the sterile solutions of the active agents (ingredients).

The dosage forms (dosage units) mentioned above as examples as well as other dosage forms are per se known, see e.g. the handbook: Remington's Pharmaceutical Sciences, Edition 18. Mack Publishing Co., Easton, USA (1990).

In the majority of cases, the pharmaceutical compositions according to the invention contain the dosage unit. For an adult person, the characteristic daily dose is 0.1 to 1000 mg of the known antivirally active agent and 0.1 to 1000 mg of a compound

of formula (I), which can be administered once or in more subdoses. The actual dose depends on several factors and is determined by the physician.

The pharmaceutical compositions of the invention are prepared by admixing the active ingredient with one or more carrier(s), and converting the mixture obtained to a pharmaceutical composition in a manner known per se. Applicable methods are known from the literature, e.g., from the above mentioned Remington's Pharmaceutical Sciences manual.

The enhanced antiviral effect of the pharmaceutical composition of the invention was investigated by testing the inhibitory effect thereof on reverse transcriptase activity of Moloney murine virus(M-MuLV). Recombinant M-MuLV reverse transcriptase was purchased from New England Biolabs, USA. Measurement of the activity was carried out by investigating the poli(rA)$_n$oligo(dT)$_{12-18}$ template-primer directed incorporation of (^{3}H)dTTP(Amersham) into the cDNS.

In each case, the final volume of the reaction mixture was 20 microliters. The composition of the reaction mixture was as follows:

2 microliters of 10x reverse transcriptase buffer,

20 microgram/ml template primer,

5 microM dTTP,

2 microCi (^{3}H)dTTP, and

the test compound (dissolved in 1x reverse transcriptase buffer solution).

The composition of the 10x reverse transcriptase buffer (1 liter of solution contains the following substances):

500 mM tris-hydrochloride / tris (hydroxy-methyl)-amino-methan-hydrochloride /(pH = 8,3),

80 mM magnesium-chloride

300 mM potassium-chloride, and

100 mM DTT (dithiotreitol).

The test materials were AZT and compound "L" added separetely or together. The reaction was initiated by adding 5U reverse transcriptase. The reaction mixture was incubated for 40 min at 37 °C. Then, 15 microliters of reaction mixture was transferred to Whatman DE81 filter-paper disc, washed by 5 % by mass of aqueous disodium-hydrogen-phosphate buffer, by water, and then with 96 % by mass of ethanol. After drying, the discs were transferred into 5 ml of scintillation liquid (OptiPhase 'HiSafe 3', Wallac), and the radioactivity of samples was measured by a Packard Tri-Carb 2200 CE liquid scintillation counter. Enzymatic activity was calculated in percent from the experimental results. Experimental results are shown in Table 1.

Table 1. Reverse transcriptase activity of Moloney murine leukemia virus

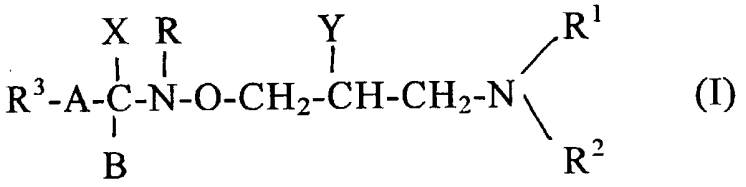
Test compounds	Activity (%)
control	100
0.1 microM/ml AZT	91
0.2 microM/ml AZT	84
0.02 mg/ml compound "L"	75
0.03 mg/ml compound "L"	74
0.1 microM/ml AZT + 0.02 mg/ml compound "L"	67
0.2 microM/ml AZT + 0.02 mg/ml compound "L"	55
0.2 microM/ml AZT + 0.03 mg/ml compound "L"	57

Retroviruses, such as HIV or the murine leukemia virus used for the above experiment, are RNA viruses. They reproduce by synthesizing DNA with their reverse transcriptase, which then becomes integrated into the genom of the host cell. As shown in Table 1., AZT by itself has only minor inhibitory effect on M-MuLV reverse transcriptase in the concentrations applied. In contrast, compound "L" has an inhibitory effect of about 25%. AZT and compound "L" decrease the enzyme activity to 55%, i.e., there is synergism between the two compounds.

Based on the above experimental results, it is concluded that the pharmaceutical compositions of the invention possesses an increased antiviral effect, therefore, it can be used for treating patients suffering from virus infection, during which the patient is treated with a known antiviral compund or its pharmaceutically acceptable acid addition salt supplemented by a hydroximic acid derivative of the formula I or a pharmaceutically acceptable acid addition salt thereof.

Claims

1. A pharmaceutical composition with an enhanced antiviral action, which comprises a known antivirally active agent or, if desired and possible, the therapeutically useful acid addition salt thereof or other therapeutically useful salt thereof and a hydroximic acid derivative of a formula (I),



(I)

wherein

R^1 means hydrogen or C_{1-5}alkyl group;

R^2 represents hydrogen; C_{1-5}alkyl group; C_{3-8}cycloalkyl group; or phenyl group optionally substituted by hydroxyl or phenyl group; or

R^1 and R^2 together with the adjacent nitrogen atom form a 5 to 8 membered ring optionally containing additional nitrogen, oxygen or sulfur atom(s); and said ring can be condensed with an other alicyclic or heterocyclic ring, preferably with benzene, naphthalene, quinoline, isoquinoline, pyridine or pyrazoline ring; furthermore if desired and possible, nitrogen and/or sulfur as heteroatom(s) are present in the form of an oxide or dioxide;

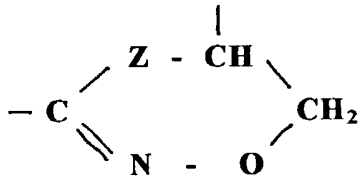
R^3 stands for hydrogen or phenyl, naphthyl or pyridyl group optionally substituted by one or more halogen(s) or C_{1-4}alkoxy group(s);

Y means hydrogen; hydroxyl group; C_{1-24}alkoxy group optionally substituted by amino group; C_{2-24}poly-alkenyloxy group containing 1 to 6 double bond(s); C_{1-25}alkanoyl group; C_{3-9} alkenoyl group; or a group of formula R^7-COO-, wherein R^7 is a C_{2-30}polyalkenyl group containing 1 to 6 double bond(s);

X represents halogen; amino group; or C_{1-4}alkoxy group;or

X and B together mean an oxygen atom; or

X and Y together with the adjacent carbon atoms and the interjacent -NR-O-CH_2- group form a ring of formula (a),



(a)

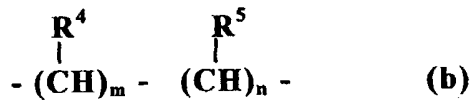
wherein

Z means oxygen or nitrogen;

R means hydrogen; or

R and B together form a chemical bond;

A stands for C_{1-4}alkylene group or a chemical bond; or a group of the formula (b),



(b)

wherein

R^4 means hydrogen; C_{1-5}alkyl group; C_{3-8}cycloalkyl group; or a phenyl group preferably substituted by halogen, C_{1-4}alkoxy or C_{1-5}alkyl group;

R^5 means hydrogen; C_{1-4}alkyl group; or a phenyl group;

m is 0, 1 or 2; and

n is 0, 1 or 2,

or a therapeutically useful acid addition salt thereof, together with one or more usual carrier(s).

2. An antivirally active pharmaceutical composition with decreased side effect(s), which comprises a known antivirally active agent or, if desired and possible, a therapeutically useful acid addition salt thereof or therapeutically useful salt thereof and a hydroximic acid derivative of formula (I),

wherein

R^1 means hydrogen or C_{1-5}alkyl group;

R^2 represents hydrogen; C_{1-5}alkyl group; C_{3-8}cycloalkyl group; or phenyl group optionally substituted by hydroxyl or phenyl group; or

R^1 and R^2 together with the adjacent nitrogen atom form a 5 to 8 membered ring optionally containing additional nitrogen, oxygen or sulfur atom(s); and said ring can be condensed with an other alicyclic or heterocyclic ring, preferably with benzene,

naphthalene, quionoline, isoquionoline, pyridine or pyrazoline ring; furthermore if desired and possible, nitrogen and/or sulfur as heteroatom(s) are present in the form of an oxide or dioxide;

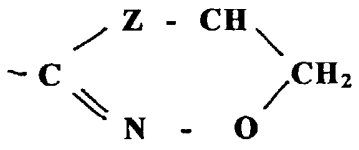
R^3 stands for hydrogen or phenyl, naphthyl or pyridyl group optionally substituted by one or more halogen(s) or C_{1-4}alkoxy group(s);

Y means hydrogen; hydroxyl group; C_{1-24}alkoxy group optionally substituted by amino group; C_{2-24}polyalkenyloxy group containing 1 to 6 double bond(s); C_{1-25}alkanoyl group; C_{3-9} alkenoyl group; or a group of formula R^7-COO-, wherein R^7 is a C_{2-30}polyalkenyl group containing 1 to 6 double bond(s);

X represents halogen; amino group; or C_{1-4}alkoxy group;or

X and B together mean an oxygen atom; or

X and Y together with the adjacent carbon atoms and the interjacent -NR-O-CH_2- group form a ring of formula (a),



(a)

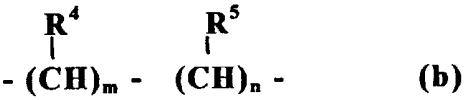
wherein

Z means oxygen or nitrogen;

R means hydrogen; or

R and B together form a chemical bond;

A stands for C_{1-4}alkylene group or a chemical bond; or a group of the formula (b),



(b)

wherein

R^4 means hydrogen; C_{1-5}alkyl group; C_{3-8}cycloalkyl group; or a phenyl group preferably substituted by halogen, C_{1-4}alkoxy or C_{1-5}alkyl group;

R^5 means hydrogen; C_{1-4}alkyl group; or a phenyl group;

m is 0, 1 or 2; and

n is 0, 1 or 2,

or a therapeutically useful acid addition salt thereof, together with one or more usual carrier(s), with the proviso that the antivirally active agent is different from zidovudine (AZT).

3. A pharmaceutical composition according to claim 1 or claim 2, which comprises

0-(3-piperidino-2-hydroxy-1-propyl)nicotinic acid amidoxime or a therapeutically useful acid addition salt thereof as a hydroximic acid derivative of formula (I).

4. A pharmaceutical composition according to claim 1 or claim 3, which comprises zidovudine (AZT) as antivirally active agent.

5. A method of treatment with an enhanced effectivity of a patient suffering from a viral infection, which comprises

administering to the patient a known antivirally active agent or a therapeutically useful acid addition salt or therapeutically useful salt thereof together with a hydroximic acid derivative of formula (I), wherein R^1, R^2, R^3, R, X, Y, A and B are as defined in claim 1, or a therapeutically useful acid addition salt thereof.

6. A method according to claim 5, which comprises using zidovudine as antivirally active agent; and 0-(3-piperidino-2-hydroxy-1-propyl)nicotinic acid amid-oxime or a therapeutically useful acid addition salt thereof as a hydroximic acid derivative of formula (I).

7. Method for decreasing the side effect(s) occurring during the treatment with an antivirally active agent of a patient suffering from viral infection, which comprises administering to the patient a known antivirally active agent or a therapeutically useful acid addition salt thereof or a therapeutically useful salt thereof together with a hydroximic acid derivative of formula (I), wherein R^1, R^2, R^3, R, X, Y, A and B are as defined in claim 2, or a therapeutically useful acid addition salt thereof, with the proviso that the known antivirally active agent is different from zidovudine (AZT).

8. Method of use of a mixture of a known antivirally active agent or a therapeutically useful acid addition salt thereof or a therapeutically useful metal salt thereof and a hydroximic acid derivative of formula (I), wherein R^1, R^2, R^3, R, X, Y, A and B are as defined in claim 1, or a therapeutically useful acid addition salt thereof, as well as optionally of one or more carrier(s) for the preparation of a pharmaceutical composition with enhanced antiviral activity.

9. Method of use of a mixture of a known antivirally active agent or a therapeutically useful acid addition salt thereof or a therapeutically useful metal salt thereof and a hydroximic acid derivative of formula (I), wherein R^1, R^2, R^3, R, X, Y, A and B are as defined in claim 2, or a therapeutically useful acid addition salt thereof, as well as optionally of one or more carrier(s) for the preparation of an antivirally active pharmaceutical composition with diminished side effect(s).

INTERNATIONAL SEARCH REPORT

national Application No
PCT/IB 98/00960

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MALLEY S.D. ET AL: "Synergistic anti-human immunodeficiency virus type 1 effect of hydroxamate compounds with 2',3'-dideoxyinosine in infected resting human lymphocytes" PROC. NATL. ACAD. SCI. U. S. A., 1994, 91/23 (11017-11021), XP000572692 USA see page 11020, column 1, paragraph 3 ---	1,2,5, 7-9
X	WO 97 13504 A (MEDGENE LIMITED;LITERATI NAGY PETER) 17 April 1997 cited in the application see page 21, paragraph 2 - page 27, paragraph 1 -----	1,4,5,8, 9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 1998	18/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 98/00960

Box I ***Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)***

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 5-7
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims
are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
In view of the very large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and the compounds specifically mentioned in the claims.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] *The additional search fees were accompanied by the applicant's protest.*

[ ] *No protest accompanied the payment of additional search fees.*

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 98/00960

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9713504 A	17-04-1997	AU 7092296 A	30-04-1997
		EP 0852495 A	15-07-1998